REMARKS

Claims 1-3 and 5-50 are pending in the present application. Claims 12-50 have been canceled without prejudice to their presentation in another application, as being drawn to non-elected inventions. Claims 1 and 5 have been amended. Claim 9 has been cancelled and replaced with new claims 51 and 52. New claims 53-59 have also been added. No new matter has been added. Upon entry of the present amendment, claims 1-3, 5-8, 10, 11, and 51-59 will be pending.

I. The Claims Are Clear And Definite

Claims 5 and 9 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Office Action asserts that there is insufficient antecedent basis for recitation of "S-mdm2 transcript" in claim 5 and "2'-O-methoxyethyl modified cytidine residue" in claim 9.

Claim 5 has been amended to more properly provide antecedent basis for "S-mdm2 transcript." Claim 9 has been canceled and replaced by new claims 51 and 52, support for which can be found throughout the specification.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

II. The Claimed Invention Is Novel

A. The Kondo I Reference

Claims 1-3 are rejected under 35 U.S.C. §102(b) as being anticipated by Kondo *et al.*, *Oncogene*, **1995**, *10*, 2001-2006 (hereinafter, the "Kondo I reference"). Claim 1 has been amended to delete "coding region" and "exon region." The Kondo I reference fails to describe an antisense compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region, or 3' untranslated region of a nucleic acid molecule encoding mdm2, wherein the antisense compound modulates the expression of mdm2.

Thus, the Kondo I reference fails to anticipate claim 1, as amended herein, and claims 2 and 3. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

B. The Chen Reference

Claims 1-3 are rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Chen *et al.*, *Proc. Nat. Acad. Sci.*, 1998, *95*, 195-200 (hereinafter, the "Chen reference"). As discussed above, claim 1 has been amended to delete "coding region" and "exon region." The Chen reference fails to describe an antisense compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region, or 3' untranslated region of a nucleic acid molecule encoding mdm2, wherein the antisense compound modulates the expression of mdm2. Thus, the Chen reference fails to anticipate claim 1, as amended herein, and claims 2 and 3. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(a) be withdrawn.

C. The Teoh Reference

Claims 1-3 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Teoh *et al.*, *Blood*, 1997, *5*, 1982-1992 (hereinafter, the "Teoh reference"). As a preliminary matter, the Teoh reference appears to have been published in about September of 1997 (see, "September 1" date on lower right corner of page 1982) and, thus, is within one year of Applicants' earliest filing date of March 26, 1998. Thus, the rejection should be more properly made under 35 U.S.C. §102(a) and not §102(b). Nevertheless, as discussed above, claim 1 has been amended to delete "coding region" and "exon region." The Teoh reference fails to describe an antisense compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region, or 3' untranslated region of a nucleic acid molecule encoding mdm2, wherein the antisense compound modulates the expression of mdm2. Thus, the Teoh reference fails

to anticipate claim 1, as amended herein, and claims 2 and 3. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

D. The Kondo II Reference

Claims 1-3 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Kondo *et al.*, *Brit. J. Cancer*, **1996**, *74*, 1263-1268 (hereinafter, the "Kondo II reference"). As discussed above, claim 1 has been amended to delete "coding region" and "exon region." The Kondo II reference fails to describe an antisense compound 8 to 30 nucleobases in length targeted to the 5'-untranslated region, intron:exon junction, intron region, translation termination codon region, or 3' untranslated region of a nucleic acid molecule encoding mdm2, wherein the antisense compound modulates the expression of mdm2. Thus, the Kondo II reference fails to anticipate claim 1, as amended herein, and claims 2 and 3. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

III. The Claimed Invention Is Not Obvious

A. The Combination Of The Burrell, Branch, and Monia References

Claims 1-3 and 6-11 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of International Application No. WO 93/20238 (hereinafter, the "Burrell reference"), Branch, *TIBS*, **1998**, *23*, 45-50 (hereinafter, the "Branch reference") and U.S. Patent No. 5,872,242 (hereinafter, the "Monia reference"). The Office Action mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to design antisense oligonucleotides having at least 17 nucleobases, as taught in the Branch reference, based upon the entire 2372 nucleobase transcript of human MDM2, as reported in the Burrell reference, and further modify the oligonucleotides to maximize target specificity, increase hybridization efficiency, and maintain nuclease resistance, as taught in the Monia reference. Applicants traverse the rejection and respectfully request reconsideration because there is no motivation to combine the cited references and, even if combined, the claimed invention would not be produced.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation **must** stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and **not** from appellants' disclosure. See for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to combine particular teachings of the cited references and achieve the claimed invention.

The only motivation identified in the Office Action for applying particular teachings of the Branch reference to the entire 2372 nucleobase transcript of human MDM2 of the Burrell reference is to design oligonucleotides having at least 17 nucleobases to "maximize target site specificity" because such sequences would have "a high probability of occurring only once in the haploid human genome" (see, Office Action at pages 10-11). This motivation, however, in no way would lead one skilled in the art to combine the teachings of these two references, let alone combine the teachings of these two references in the manner suggested in the Office Action. Whether or not the claimed compounds hybridize only to mdm2 nucleic acid molecules and/or modulate the expression of only

MDM2 (*i.e.*, maximize target site specificity) is irrelevant. Indeed, Applicants' claims do not recite or require any amount of target specificity for the antisense compounds. Thus, the only motivating force the Office Action attributes to the Branch reference is not a motivating force that would **impel** one skilled in the art to do what Applicants have done. Thus, the Branch reference does not provide the requisite motivating force.

It appears that the Office Action has picked one particular element from the Burrell reference (the entire 2372 nucleobase transcript of human MDM2), one particular element from the Branch reference (at least 17 nucleobases) and particular elements from the Monia reference (oligonucleotide modifications) from the many elements recited in the references and combined the selected elements in a specific manner. Indeed, it appears that the only guide to picking and choosing particular elements from the cited references appears to have been the present application. Thus, the combination of cited references is improper for its use of hindsight reconstruction based upon Applicant's disclosure. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

The Federal Circuit has recently affirmed the requirement for motivation to combine references, stating that:

> virtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed [**10] elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention . . .
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and ***with no knowledge of the claimed invention***, would select the elements from the cited prior art references for combination in the manner claimed . . .

> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Yamanouchi Pharm. Co. v. Danbury Pharm, Inc., 231 F.3d 1339 (Fed. Cir. 2000); 56 U.S.P.Q.2d 1641, 1645, citing *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 U.S.P.Q.2d 1453, 1457-8 (Fed. Cir. 1998) (emphasis added).

The general statement that it would be obvious to combine teachings of particular references to design antisense oligonucleotides is unavailing. Such a statement, at best, is an invitation for further experimentation and, at most, provides an "obvious to try" situation. However, "obvious to try" is not the standard of 35 U.S.C. §103. *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987).

Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

B. The Combination Of The Chen, Teoh, Kondo I, Or Kondo II Reference With The Monia Reference

Claims 1-3 and 6-11 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over any of the Chen, Teoh, Kondo I, or Kondo II references in view of the Monia reference. As discussed above, claim 1 has been amended and, thus, the Chen, Teoh, Kondo I, and Kondo II references do not anticipate the claimed invention. Further, the Monia reference does not cure the deficiencies of the cited references. Indeed, the Monia reference does not teach or suggest any antisense compound targeted to any region of mdm2. Thus, the present rejection has been rendered moot by the amendment of claim 1.

Applicants have added new claims 53-59, which are directed to antisense compound 8 to 30 nucleobases in length targeted to the coding region or exon region of a nucleic acid molecule encoding mdm2, wherein the antisense compound is a chimeric phosphorothioate oligonucleotide comprising 2'-methoxyethyl wings and a deoxy gap, and wherein the antisense compound inhibits mdm2 expression by at least 60%, support for which can be found at, for example, Example 15 of

the specification. To the extent that the present rejection is applied to new claims 53-61, Applicants submit that there is no motivation to combine the cited references in such a manner to produce the claimed compounds. Any such motivation, at most, amounts to an obvious to try situation.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

III. Obviousness-Type Double Patenting

Claims 1-3 and 6-11 are rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-8 of U.S. Patent No. 6,248,921 (hereinafter, the "'921 patent") and over claims 1-20 of U.S. Patent 6,184,212 (hereinafter, the "'212 patent"). Applicants traverse this rejection and respectfully request reconsideration because the claimed invention is not obvious.

The Office Action asserts that the '921 patent and the '212 patent each disclose species of oligonucleotides targeting human mdm2 and that claims 1-3 and 6-11 of the present application are directed to a broader genus comprising compounds that are also targeted to human mdm2. The Office Action mistakenly concludes that because a species anticipates a genus, the subject matter of claims 1-3 and 6-11 of the present application is obvious in view of the cited claims of the '921 and '212' patents. The Office Action cites MPEP § 2131.02 for support. The analysis carried out in the Office Action, however, is unavailing for several reasons.

As a preliminary matter, MPEP § 2131.02 does not provide the correct standard for the purposes of an obviousness-type double patenting analysis. Rather, MPEP § 2131.02 is appropriate when considering the anticipation of an invention by the prior art. Indeed, the very last sentence of that section states (referring to the *In re Gostelli* case discussed therein) that a species would indeed anticipate the genus "unless applicant was entitled to his foreign priority date." Applicants remind the Examiner that both the '921 patent and the '212 patent have the same priority date as the present application. Thus, neither the '921 patent nor the '212 patent are prior art for purposes of an anticipation rejection as discussed in MPEP § 2131.02, let alone an obviousness rejection.

What the Examiner appears to suggest is that simply because a compound claimed by the issued patents falls within a broad claim or claims of the present patent application, an obviousness-type double patenting rejection is warranted. However, this is not the law. An obviousness-type double patenting rejection is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. §103. *In re Braithwaite*, 154 U.S.P.Q. 29, 34 (C.C.P.A. 1967) and *In re Longi*, 225 U.S.P.Q. 645, 648 n.4 (Fed. Cir. 1985). Thus, under the law, the pivotal question in an obviousness-type double patenting analysis is: Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent? *In re Vogel*, 164 U.S.P.Q. 619 (C.C.P.A. 1970). If the answer to this question is no, there can be no double patenting. In making this analysis, then, the proper inquiry is as taught in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). See, M.P.E.P. §804. **A determination whether one patent application is generic to another patent is not the appropriate inquiry.** The following quotation from *In re Kaplan*, 229 U.S.P.Q. 678 (Fed. Cir. 1986) is instructive:

> By domination we refer ... to that phenomenon ... whereunder one patent has a broad or "generic" claim which "reads on" an invention defined by another narrower or more specific claim in another patent, the former "dominating" the latter because the more narrowly claimed invention cannot be practiced without infringing the broader claim ... In possibly, simpler terms, one patent dominates another if a claim of the first patent reads on a device built or process practiced according to the second patent disclosure. This commonplace situation **is not**, *per se*, double patenting as the board seems to think. (citations omitted; emphasis added).

Thus, that some of '921 patent's claimed compounds and some of the '212 patent's claimed compounds may also meet limitations of claims in the present patent applications is not grounds for an obviousness-type double patenting rejection. It is simply a case of one patent application dominating another patent. Domination by itself cannot support a double patenting rejection. Further, the proper analysis has not even been carried out. Thus, the obviousness-type double patenting rejections are misplaced.

In view of the foregoing, Applicants respectfully request that the rejections under the doctrine of obviousness-type double patenting be withdrawn.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6914 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,

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